



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/70, A61L 15/44	A1	(11) International Publication Number: WO 95/23596 (43) International Publication Date: 8 September 1995 (08.09.95)
<p>(21) International Application Number: PCT/EP95/00791</p> <p>(22) International Filing Date: 2 March 1995 (02.03.95)</p> <p>(30) Priority Data: 9404248.8 5 March 1994 (05.03.94) GB</p> <p>(71) Applicant (for all designated States except US): THE BOOTS COMPANY PLC [GB/GB]; 1 Thane Road West, Nottingham NG2 3AA (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): AGGARWAL, Meena [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). HAGUE, John, Neville [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). KHAN, Karrar, Ahmad [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). SMITH, Alan [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB).</p> <p>(74) Agent: MILLER, Thomas, Kerr; The Boots Company plc, Patents Dept., R4 Pennyfoot Street, Nottingham NG2 3AA (GB).</p>	<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: ADHESIVE FREE TOPICAL PHARMACEUTICAL FORMULATIONS</p> <p>(57) Abstract</p> <p>An adhesive-free topical pharmaceutical formulation comprising an absorbent material wherein the absorbent material is impregnated with a pharmaceutical composition comprising a solution of a non-steroidal anti-inflammatory drug in a C₂₋₄ alcohol. Suitably the non-steroidal anti-inflammatory drug comprises ibuprofen, S(+)-ibuprofen, flurbiprofen, S(+)-flurbiprofen, R(-)-flurbiprofen, ketoprofen, S(+)-ketoprofen, piroxicam, or naproxen, including pharmaceutically acceptable salts of each and comprises 0.1-25 % by weight of the pharmaceutical composition. The C₂₋₄ alcohol comprises 20-95 % by weight of the pharmaceutical composition. The pharmaceutical composition further comprises 0.01-90 % by weight of a co-solvent selected from propylene glycol, benzyl alcohol, isopropyl palmitate, isopropyl myristate, or polyvinylpyrrolidone. The formulation is preferably in the form of a wipe or a wrap-around. The formulations are useful for the local treatment of pain and inflammation.</p>		

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

Adhesive free topical pharmaceutical formulations

The present invention relates to novel topical pharmaceutical formulations, comprising a non-steroidal antiinflammatory drug (NSAID). The formulations may be
5 used for the local treatment of pain and inflammation.

Topical formulations of NSAIDs, in the form of patches which are adhered to the skin, are known. However, the removal of these patches may traumatise the skin and cause discomfort to the patient. In addition
10 the drug may interact with the adhesive thus making it difficult to determine the actual dose received by the patient.

US 4,704,406 discloses sprayable preparations for the topical application of non-steroidal anti-inflammatory agents comprising a) a volatile solvent
15 which may be ethanol, propanol or isopropanol and b) a non-volatile solvent which may be a polyfunctional alcohol or a fatty acid ester of a mono- or polyfunctional alcohol, the weight ratio of a:b being
20 from about 1:1 to 20:1. However, these formulations suffer from the disadvantage that NSAIDs are irritant if inhaled.

WO 92/05768 discloses the use of S(+)-flurbiprofen in the prevention or treatment of sunburn. On page 16
25 lines 15 to 21 it is stated that the drug may be applied topically in any fashion suitable for topical administration. A clothwipe and an impregnated bandage are listed as two, amongst many, typical topical preparations. No specific examples of such formulations
30 are disclosed and the only assistance which the skilled reader is given is a reference to a textbook - Remington's Pharmaceutical Sciences, 17th Edition 1985.

- 2 -

However, this textbook gives no practical assistance in how to formulate a clothwipe or an impregnated bandage. Even with the incorporation of this reference the disclosure in WO 92/05768 is not enabling.

5 The present invention provides an adhesive-free topical pharmaceutical formulation comprising an absorbent material wherein the absorbent material is impregnated with a pharmaceutical composition comprising a solution of a non-steroidal anti-inflammatory drug in
10 a C₂₋₄ alcohol.

The term adhesive-free means that the formulation does not contain an adhesive (for example a silicone based adhesive or an acrylate based adhesive) to hold the absorbent material in contact with the skin.

15 Such formulations are particularly useful in the treatment of pain and inflammation associated with soft-tissue and musculo-skeletal injuries e.g. sports injuries. The formulations are also useful as a supportive treatment in localised arthritic, rheumatic
20 and inflammatory conditions. They are convenient to use, especially over large skin areas with a high density of hair and provide an immediate localised soothing and cooling effect due to evaporation of the alcohol as the drug begins to have its pharmacological
25 effect.

The topical application of the pharmaceutical composition as a solution has the potential advantages of improved penetration and better physical and chemical stability due to the relatively small number of
30 excipients required.

Suitably the absorbent material may comprise any natural or synthetic material which is pharmaceutically acceptable. Preferably the absorbent material comprises lint, compressed cotton, paper, cotton wool, gauze, 5 woven or unwoven fabric or fabric which has been spun. More preferably, the absorbent material comprises compressed tissue paper, compressed cotton wool, polyester or a viscose/polyester mixture.

Suitable C₂₋₄ alcohols are ethanol, propanol, 10 isopropanol or n-butanol, isobutanol, sec-butanol or tert-butanol. Preferably ethanol is used. Suitably the C₂₋₄ alcohol comprises 20-95% by weight of the pharmaceutical composition.

Suitably the non-steroidal antiinflammatory drug 15 comprises ibuprofen, S(+)-ibuprofen, flurbiprofen, S(+)-flurbiprofen, R(-)-flurbiprofen, ketoprofen, S(+)-ketoprofen, piroxicam, or naproxen, including pharmaceutically acceptable salts of each. Preferably the non-steroidal antiinflammatory drug is ibuprofen, 20 S(+)-ibuprofen, flurbiprofen or S(+)-flurbiprofen. Most preferably S(+)-flurbiprofen is used.

Typically the non-steroidal antiinflammatory drug comprises 0.1-25% by weight of the pharmaceutical composition, for example 0.1-15%. Preferably the non- 25 steroidal drug comprises 1-15%, for example 1-10%, by weight of the pharmaceutical composition, more preferably 2.5 to 7.5% by weight and most preferably 4 to 6% by weight of the pharmaceutical composition.

Preferably the pharmaceutical composition comprises 30 one or more co-solvents. The co-solvents are selected and optimised to achieve the desired consistency and skin-feel and to maximise the absorption of the active

- 4 -

ingredient. Suitable co-solvents are pharmaceutically acceptable excipients for the NSAID or salt thereof which are less-volatile than the C₂₋₄ alcohol and which prevent crystallisation of the NSAID despite evaporation of the C₂₋₄ alcohol. Suitable co-solvents are C₂₋₄ alkanediols (for example 1,3-butanediol, 2,3-butanediol, 1,2-propanediol, 1,3-propanediol), benzyl alcohol, fatty acid esters (such as isopropyl palmitate or isopropyl myristate) or polyvinylpyrrolidone.

Suitably the co-solvent comprises 0.01 to 90% by weight of the composition. Preferred co-solvents are propylene glycol, benzyl alcohol, isopropyl palmitate, isopropyl myristate, or polyvinylpyrrolidone. Suitably benzyl alcohol comprises 1-15% by weight of the pharmaceutical composition and preferably comprises 2-10% by weight of the pharmaceutical composition. Suitably propylene glycol comprises 1-25% by weight of the pharmaceutical composition and preferably comprises 10-20% by weight of the pharmaceutical composition.

A particularly preferred co-solvent is polyvinylpyrrolidone. Surprisingly polyvinylpyrrolidone has been found to form an amorphous matrix with NSAIDs, particularly with flurbiprofen or ibuprofen, or their respective S(+)-enantiomers, when an ethanolic solution is evaporated. An amorphous matrix may also be formed by mixing or melting the NSAID with polyvinylpyrrolidone. The optimum amount of polyvinylpyrrolidone required for each NSAID may be found by construction of a phase diagram, for example by plotting the melting point (using Differential Scanning Calorimetry) or solubility against the percentage weight of each of the components in the mixture, by methods known to those skilled in the art.

- 5 -

Suitably the polyvinylpyrrolidone comprises 0.01 to 25% by weight of the pharmaceutical composition. Preferably the polyvinylpyrrolidone comprises 0.05 to 10% by weight of the pharmaceutical composition and more preferably the polyvinylpyrrolidone comprises 0.25 to 1.5% by weight of the pharmaceutical composition.

A preferred pharmaceutical composition comprises:
1-10% by weight of S(+)-flurbiprofen;
0.1-10% by weight of polyvinylpyrrolidone; and
10 80-98.9% by weight of ethanol.

Other particularly preferred co-solvents are fatty acid esters. The use of these co-solvents in high concentration, for example greater than 50% by weight of the pharmaceutical composition, produces an advantageous emollient effect and reduces undesirable drying of the skin. Suitably the fatty acid ester comprises 1 to 90% by weight of the pharmaceutical composition. Preferably the weight of the fatty acid ester in the composition is greater than the weight of the C₂₋₄ alcohol. More preferably the fatty acid ester comprises 50 to 90% by weight of the pharmaceutical composition and most preferably comprises 50 to 70% by weight of the pharmaceutical composition. Preferred fatty acid esters are isopropyl palmitate and isopropyl myristate. More preferably the fatty acid ester is isopropyl palmitate.

A preferred pharmaceutical composition comprises:
1-10% by weight of S(+)-flurbiprofen;
1-10% by weight of benzyl alcohol;
50-70% by weight of isopropyl palmitate; and
30 10-48% by weight of ethanol.

Optionally the pharmaceutical composition comprises one or more penetration enhancers for example an

- 6 -

aromatic oil (for example peppermint oil or eucalyptus oil), a dialkyl sulphoxide, an amide of the cyclic amine, polyoxyethylene (2) oleyl ether (available from ICI Surfactants under the trade name BRIJ 92), a fatty acid (for example oleic acid), a fatty alcohol (for example lauryl alcohol), methyl salicylate, diethylene glycol or a surfactant. Suitably the penetration enhancer comprises 0.1-10% by weight of the pharmaceutical composition and preferably comprises 0.5 to 5% by weight of the pharmaceutical composition.

Optionally the pharmaceutical composition may contain a thickener, such as hydroxypropyl cellulose (available from Aqualon under the trade name Klucel). Suitably the thickener comprises 0.1 to 25% by weight of the pharmaceutical composition, preferably 0.1-5% by weight.

Optionally the pharmaceutical composition may contain a stabiliser to reduce esterification reactions between the C₂₋₄ alcohol and the NSAID where the NSAID is a carboxylic acid. Water is a suitable stabiliser when it comprises 5 to 30% by weight of the pharmaceutical composition.

Optionally the pharmaceutical composition may comprise a pharmaceutically acceptable rubefacient to provide a localised warming effect. Suitably the rubefacient comprises 0.01-10% by weight of the composition. Preferably the rubefacient comprises eucalyptus oil (1-5% by weight), capsaicin (0.01-0.1% by weight), or methyl salicylate (3-7% by weight), ethyl nicotinate (0.01 - 1% by weight) or nicotinic acid (0.01-1% by weight).

- 7 -

Optionally the pharmaceutical composition may comprise a film forming agent such as cetostearyl alcohol. Suitably the film former comprises 0.1 to 10% by weight of the pharmaceutical composition and preferably comprises 0.5 to 5% by weight of the pharmaceutical composition.

Optionally the pharmaceutical composition may also comprise a topically acceptable steroid, for example prednisolone, hydrocortisone, prednisone, dexamethasone, triamcinilone, betamethasone, beclomethasone, desoxymethasone, diflucorolone, fluclorolone, fluocinolone and fluorcinonide. It will be appreciated by those skilled in the art that esters or other pharmaceutically acceptable derivatives of the above steroids may also be used. Suitably the steroid comprises 0.001 to 5.0% by weight of the pharmaceutical composition, preferably 0.01 to 2.5% by weight and more preferably 0.02 to 0.5% by weight of the pharmaceutical composition.

In another aspect the present invention comprises a process for the preparation of a pharmaceutical composition, as described above, comprising combining the NSAID or a salt thereof with the C₂₋₄ alcohol and optional ingredients, for example the co-solvent, with suitable mixing. Any mixing method known to those skilled in the art may be employed, for example stirring, shaking or other methods of mechanical agitation.

The pharmaceutical compositions may additionally comprise other components well known to those skilled in the art. Such additional ingredients may comprise one or more of the following and/or any mixtures thereof: sequestrants (for example tetra sodium ethylene diamine

- 8 -

tetra acetate dihydrate), anti-oxidants (for example DL α tocopherol acetate and/or butylated hydroxytoluene), preservatives (for example bronopol, sodium dehydroacetate, polyhexamethylenebiguanide hydrochloride, isothiazolonediazolidinylurea, and/or 2-phenoxyethanol), colouring agents (for example pharmaceutically acceptable and/or food desirable colorants and/or dyes), emollients (for example mineral oils, polymethylsiloxane, dimethicone, volatile silicone fluid, sweet almond oils, petroleum jellys and/or triglycerides of fatty acids [such as lauric triglyceride, capric/caprylic triglyceride, and/or mixed triglycerides]), moisturisers (for example D-panthenol), perfumes (for example pharmaceutically and/or cosmetically acceptable sweet smelling oils) and humectants to improve the feel of the composition on the skin.

The partitioning potential of the pharmacologically active ingredient from the pharmaceutical composition may be optimised by examining the solubility of the active ingredient in the residual pharmaceutical composition which is obtained after evaporation of the C₂₋₄ alcohol. In order to obtain maximum skin penetration it is believed that the active ingredient should be in solution at near-saturation in the residual pharmaceutical composition. Preferably the active ingredient should be at saturation in the residual pharmaceutical composition and most preferably the active ingredient should be at super-saturation in the residual pharmaceutical composition. Therefore, for optimal absorption, the excipients and their proportions must be adjusted to achieve the desired level of saturation of the active ingredient on the skin after the evaporation of the volatile components.

An initial optimisation may be carried out by adjusting the relative amounts of the excipients and then applying the pharmaceutical composition to a glass slide. After a suitable time interval the composition is examined under a microscope for signs of crystallisation of the active.

Alternatively the relative amounts of volatile and non-volatile components may be adjusted and the solubility of the active ingredient determined. Using these results phase diagrams may be constructed which may be used to obtain the optimum level of saturation required for maximum skin penetration

Skin penetration may be further optimised by examining the penetration of the active ingredient from test compositions or formulations through a suitable membrane, for example human cadaver skin [see Int.J.Pharm. 87, 261-264 (1992)], or hairless mouse skin [see J.Pharm.Pharmacol, 40, 525-529 (1987)], in a diffusion cell.

Suitably a horizontal diffusion cell may be used with the membrane being placed as a barrier between two halves (a donor compartment and a receptor compartment) of the diffusion cell. A specified amount of the formulation is applied to one side (the donor compartment) of the membrane which is maintained at a suitable temperature e.g. 32°C. The donor compartment contains a suitable receptor solution continuously agitated and maintained at the desired temperature. After application of the test composition or test formulation the receptor medium in the receptor compartment is sampled at specific time points, optionally replacing the medium as required. The samples are analysed for content of the active

- 10 -

ingredient using appropriate qualitative analytical techniques, for example HPLC. Using the assay results, taking into account the area available for diffusion, the volume of the receptor compartment, the receptor sample volumes, the amount of active ingredient absorbed per unit area and the percentage of the initial dose which has permeated can be calculated, and absorption profiles constructed. A suitable number of replicates should be performed.

10 Suitably the pharmaceutical formulation may be in the form of a disposable wipe. The wipe may be contained in a suitable impermeable pouch to prevent evaporation on storage. As the name suggests, the wipe is wiped over the affected area so that the drug dose is
15 applied to the skin in solution, the wipe being discarded after use. If desired the wipe may be held in contact with the affected area of the skin by any suitable means, for example by hand or by means of a bandage. Optionally an impermeable backing layer may be
20 present on one side of the wipe. Use of an impermeable backing layer reduces hand-drug contact. The formulation should provide high penetration rates, since the NSAID or salt thereof remains in solution in the co-solvent on the skin, and a cooling effect. The
25 impermeable backing layer may be joined to the absorbent material at the edges or all over the surface. Optionally the impermeable backing layer may be provided with pockets. The purpose of the pockets is to receive the thumb and fingers of the person applying to wipe to
30 facilitate administration and minimise hand-drug contact.

- Suitably the surface of the wipe for application to the skin has an area in the range 5-500cm², preferably in the range 5-100 cm² and more preferably in the range

- 11 -

10-40 cm². The dosage of the non-steroidal antiinflammatory drug applied to the skin is in the range of 0.5 mg to 10 mg per cm² of absorbent material in contact with the skin. Preferably the dosage is in the range 1-5 mg per cm² and more preferably the dosage is in the range 2-4 mg per cm². The shape of the wipe is unimportant but preferably it is square, circular or rectangular, or dumb-bell shaped. Suitably the density of the absorbent material used lies in the range of 20-300 g/m², for example 40-200 g/m², preferably in the range 30-200 g/m², for example 50-120 g/m² and most preferably the density lies in the range of 60-180 g/m², for example 60-100 g/m².

Alternatively, the formulation may be provided in the form of a wrap-around tissue which may be applied to joints, for example knees, ankles or elbows. The wrap around tissue allows the active drug solution to remain in contact with the skin for a longer period. Optionally an impermeable backing layer may be present on one side of the tissue. The fabric is wrapped around the affected area, for example a joint, and optionally may be secured by an additional bandage (such as Setonet), such that the impermeable backing layer is in contact with the bandage, and removed after a period of time.

Suitably the surface of the wrap-around tissue for application to the skin has an area in the range 100-500 cm² and preferably in the range 200-300 cm². The dosage ranges of non-steroidal anti-inflammatory drugs per cm² of absorbent material are as described for the wipe. Suitably the density of the absorbent material used lies in the range of 20-300 g/m², for example 40-200 g/m², preferably in the range 30-200 g/m², for example 50-120 g/m² and most preferably

- 12 -

the density lies in the range of 60-180 g/m², for example 60-100 g/m².

The shape of the wrap-around is suitably circular, square, rectangular or shaped to facilitate comfortable application to a joint for example a butterfly shape or a dumb-bell shape. Preferably the wrap-around is shaped for easy application to a knee, ankle, elbow, wrist, finger or toe joint.

Suitable impermeable backing material comprises a flexible polymer which is impermeable to the solvents used in the pharmaceutical compositions such as polyethylene or polypropylene. Preferably the backing material is polyethylene.

The pharmaceutical formulations are prepared by cutting the absorbent material to an appropriate size, providing the material with an impermeable backing if desired and then contacting the absorbent material with the pharmaceutical composition such that the pharmaceutical composition is absorbed into the material (the latter two steps may also be carried out before cutting the absorbent material to size). Contact may be made by dipping the material into the pharmaceutical composition, spraying the pharmaceutical composition onto the material or spreading the pharmaceutical composition over the material. Alternatively the absorbent material may be placed in an impermeable pouch which is open at one end and the pharmaceutical composition added. The pouch is then sealed. The pouch may be formed from a material which is impermeable to the pharmaceutical composition for example metal foil or a flexible polymer.

One preferred embodiment according to the present invention comprises an absorbent material, without adhesive, suitable for use as wipe having a first surface, to be placed in contact with the skin, with an area in the range of 10-40 cm², wherein the absorbent material is impregnated with a pharmaceutical composition comprising 2.5-7.5% by weight of a solution of S(+)-flurbiprofen in ethanol containing 0.1-10% of a co-solvent such that the effective dose is in the range 0.5 to 10 mg per cm² of absorbent material in contact with the skin and wherein the absorbent material has a second surface, opposite the first, provided with an impermeable backing layer of polyethylene, and further wherein the absorbent material is sealed in an impermeable pouch.

A second preferred embodiment comprises an absorbent material, without adhesive, suitable for use as a wrap-around having a first surface, to be placed in contact with the skin, with an area in the range of 200-300 cm², wherein the absorbent material is impregnated with a pharmaceutical composition comprising a 2.5-7.5% by weight of a solution of S(+)-flurbiprofen in ethanol containing 0.1-10% of a co-solvent such that the effective dose is in the range 0.5 to 10 mg per cm² of absorbent material in contact with the skin and wherein the absorbent material has a second surface, opposite the first, provided with an impermeable backing layer of polyethylene, and further wherein the absorbent material is sealed in an impermeable pouch. Preferably the backing layer is provided with pockets.

The invention is illustrated by way of example only in Figures 1-8.

- 14 -

Fig.1 shows a plan view of a rectangular wipe with pockets;

Fig.2 shows a cross-sectional view about the axis shown in Fig.1;

5 Fig.3 & 4 show alternative shapes of wipes with pockets;

Fig.5 shows a wipe in use;

Fig.6 & 7 show examples of a wrap-around and product;

Fig.8 shows a cross-section of a wrap around product.

10 Figure 2 shows a wipe comprising an absorbent layer (1) with an impermeable backing layer (2) provided with pockets (3) for insertion of the thumb and fingers as shown in Figure 5.

Figure 8 shows a cross-section of a wrap-around
15 product comprising an absorbent layer (4) and an impermeable backing layer (5).

The invention is illustrated by the following non-limitative Examples.

The NSAID's used in this invention are commercially
20 available or may be prepared by known methods. For example racemic ibuprofen, racemic flurbiprofen, S(+)-ibuprofen and S(+)-flurbiprofen may be obtained from the Boots Company PLC. S(+)-Ibuprofen and S(+)-flurbiprofen may also be obtained by resolving the
25 racemic acids by methods known to those skilled in the art, for example using α -methylbenzylamine.

COMPOSITIONSComposition 1

		<u>% w/w</u>
	S(+)-Flurbiprofen	5
5	Benzyl Alcohol	5
	Cetostearyl Alcohol	2
	Denatured Ethanol	to 100%

Composition 2

		<u>% w/w</u>
	S(+)-Flurbiprofen	5
10	Benzyl Alcohol	2
	Cetostearyl Alcohol	2
	Denatured Ethanol	to 100%

Composition 3

		<u>% w/w</u>
	S(+)-Flurbiprofen	5
15	Benzyl Alcohol	5
	Propylene Glycol	1
	Denatured Ethanol	to 100%

20 Composition 4

		<u>% w/w</u>
	S(+)-Flurbiprofen	5
	Propylene Glycol	10
	Benzyl Alcohol	5
25	Ethanol	to 100%

- 16 -

Composition 5

	<u>% w/w</u>
S(+)-Flurbiprofen	5
Benzyl Alcohol	5
5 Cetostearyl Alcohol	2
Ethanol	to 100%

The cetostearyl alcohol was dissolved in most of the ethanol. Benzyl alcohol was added to the mixture. The flurbiprofen was dissolved in the mixture. The mixture
10 was made up to weight with ethanol.

Composition 6

	<u>% w/w</u>
S(+)-Flurbiprofen	5
Propylene Glycol	10
15 Isopropyl Palmitate	3
Ethanol	to 100%

Composition 7

	<u>% w/w</u>
S(+)-Flurbiprofen	5
20 Polyvinylpyrrolidone (K30)	1
Isopropyl Myristate	3
Ethanol	to 100%

Composition 8

	<u>% w/w</u>
25 S(+)-Flurbiprofen	5
Polyvinylpyrrolidone (K30)	1.0
Volatile Silicone	1.5
Ethanol	to 100%

- 17 -

Composition 9

	<u>% w/w</u>
S(+)-Flurbiprofen	5
Propylene Glycol	15
5 Benzyl Alcohol	10
Ethanol	to 100%

Composition 10

	<u>% w/w</u>
S(+)-Flurbiprofen	5
10 Brij 92	3
Propylene Glycol	10
Ethanol	to 100%

Composition 11

	<u>% w/w</u>
15 S(+)-Flurbiprofen	5
Polyvinylpyrrolidone (K90)	1
Ethanol	to 100%

Composition 12

	<u>% w/w</u>
20 S(+)-Flurbiprofen	5
Polyvinylpyrrolidone (K90)	0.56
Ethanol	to 100%

Composition 13

	<u>% w/w</u>
25 S(+)-Flurbiprofen	5
Polyvinylpyrrolidone (K90)	0.26
Ethanol	to 100%

- 18 -

Composition 14

	<u>% w/w</u>
S(+)-Flurbiprofen	5
Polyvinylpyrrolidone (K90)	0.1
5 Ethanol	to 100%

Composition 15

	<u>% w/w</u>
S(+)-Flurbiprofen	5
Polyvinylpyrrolidone (K30)	0.56
10 Ethanol	to 100%

The flurbiprofen and polyvinylpyrrolidone were formed into a clear, amorphous, mass with some of the ethanol. The mass was made up to weight with the remaining ethanol.

15 Composition 16

	<u>% w/w</u>
S(+)-Flurbiprofen	5
Polyvinylpyrrolidone (K30)	0.26
Ethanol	to 100%

20 Composition 17

	<u>% w/w</u>
S(+)-Flurbiprofen	5
Polyvinylpyrrolidone (K30)	0.1
Ethanol	to 100%

- 19 -

Composition 18

	<u>% w/w</u>
S(+)-Flurbiprofen	5
Propylene Glycol	20
5 Ethanol	to 100%

Composition 19

	<u>% w/w</u>
S(+)-Flurbiprofen	5
Isopropyl Palmitate	60
10 Eucalyptus Oil	3
Benzyl Alcohol	5
Brij 92	3
Ethanol	to 100%

Composition 20

	<u>% w/w</u>
15 S(+)-Flurbiprofen	5
Benzyl Alcohol	5
Isopropyl Palmitate	60
Ethanol	to 100%

- 20 The flurbiprofen and isopropyl palmitate were mixed and agitated to form a suspension. Benzyl alcohol was added to dissolve most of the flurbiprofen. The mixture was made up to weight with the ethanol.

Composition 21

	<u>% w/w</u>
25 S(+)-Flurbiprofen	2.5
Benzyl Alcohol	3
Isopropyl Palmitate	56
Brij 92	3
30 Eucalyptus Oil	3
Ethanol	to 100%

- 20 -

The flurbiprofen and isopropyl palmitate were mixed and agitated to form a suspension. Benzyl alcohol and Brij 92 were added to completely dissolve the flurbiprofen, followed by the eucalyptus oil. The mixture was made up to weight with ethanol.

Composition 22

	<u>% w/w</u>
S(+)-Flurbiprofen	5
Klucel GF	0.5
10 Propylene Glycol	2
Brij 92	1
Purified Water	10
Ethanol	to 100%

The Brij 92, propylene glycol and ethanol were mixed. Flurbiprofen was dissolved into the mixture. The Klucel was added and mixed until homogenous. The water was added slowly and stirred until a homogenous solution was obtained. Finally the solution was made up to weight with ethanol.

20 Composition 23

	<u>% w/w</u>
S(+)-Flurbiprofen	10
Benzyl Alcohol BP	10
Eucalyptus Oil BP	3
25 Klucel GF	0.3
PVP	2
Dimethicone	1
Ethanol	to 100%

In Compositions 1-23 the ingredients were mixed together to form a solution, unless otherwise stated.

- 21 -

Additional Examples are prepared by replacing S(+)-flurbiprofen by S(+)-ibuprofen, S(+)-ketoprofen, racemic flurbiprofen, racemic ibuprofen or racemic ketoprofen each of which may be present in amounts of 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9% or 10% by weight. Similar % amounts of S(+)-flurbiprofen may also be used.

Example 1 (Wipe)

A circular piece of unwoven fabric which had a diameter of approximately 5 cm and a density of 80 g/m² was placed in a foil pouch open at one end. Composition 1 (1 ml) was added to the pouch and the pouch was sealed.

Example 2 (Wrap-Around)

A paper tissue, in which the surface area of the side to be placed on a joint was 250 cm² and the density of the material was 23 g/m², was placed in a foil pouch open at one end. Composition 1 (2 ml) was added and the pouch was sealed.

A fabric suitable for use in the above formulations comprises non-woven wet-laid fabric composed of wood pulp/viscose fibres bonded with ethyl vinyl acetate binder having the following specification:

Weight: 43 - 47 gsm

Thickness: 200 - 240 microns

Tensile Strength Dry MD 1200 - 1500 N/M
(Newtons/Metre)

CD 800 - 1100 N/M

Wet MD 500 - 800 N/M

CD 350 - 600 N/M

- 22 -

Stretch	Dry MD	7 - 10%
	CD	8 - 13%
	Wet MD	12 - 20%
	CD	15 - 22%

5 Absorption capacity 250 g/m²

Sheet Size: 230 x 250 mm ± 5 mm J-folded

Sheet Count: 20 nominal

Other suitable fabrics include viscose (density 45 g/m²), chemically bonded viscose (density 40 g/m²), a
10 mixture of viscose (67%) and polyester (33%) (density 65 g/m²), and polyester (density 171 g/m²).

CLAIMS

1. An adhesive-free topical pharmaceutical formulation comprising an absorbent material wherein the absorbent material is impregnated with a pharmaceutical composition comprising a solution of a non-steroidal anti-inflammatory drug in a C₂₋₄ alcohol.

2. A formulation according to claim 1 wherein the non-steroidal anti-inflammatory drug is ibuprofen, S(+)-ibuprofen, flurbiprofen, S(+)-flurbiprofen, R(-)-flurbiprofen, ketoprofen, S(+)-ketoprofen, piroxicam, or naproxen, including pharmaceutically acceptable salts of each and comprises 0.1-25% by weight of the pharmaceutical composition.

3. A formulation according to either claim 1 or claim 2 wherein the C₂₋₄ alcohol is selected from ethanol, propanol, isopropanol or n-butanol, isobutanol, sec-butanol or tert-butanol and comprises 20-95% by weight of the pharmaceutical composition.

4. A formulation according to any previous claim wherein the pharmaceutical composition further comprises 0.01-90% by weight of a co-solvent selected from propylene glycol, benzyl alcohol, isopropyl palmitate, isopropyl myristate, or polyvinylpyrrolidone.

5. A formulation according to claim 4 wherein the co-solvent is polyvinylpyrrolidone and comprises 0.01 to 25% by weight of the pharmaceutical composition.

- 24 -

6. A formulation according to claim 5 wherein the pharmaceutical composition comprises:

1-10% by weight of S(+)-flurbiprofen;

0.1-10% by weight of polyvinylpyrrolidone; and

5 80-98.9% by weight of ethanol.

7. A formulation according to claim 4 wherein the co-solvent is isopropyl palmitate and comprises greater than 50% by weight of the pharmaceutical composition.

8. A formulation according to claim 7 wherein the pharmaceutical composition comprises:

1-10% by weight of S(+)-flurbiprofen;

1-10% by weight of benzyl alcohol;

50-70% by weight of isopropyl palmitate; and

10-48% by weight of ethanol.

15 9. A formulation as claimed in claim 1 suitable for use as wipe having a first surface, to be placed in contact with the skin, with an area in the range of 10-40 cm², wherein the absorbent material is impregnated with a pharmaceutical composition comprising 2.5-7.5% by

20 weight of a solution of S(+)-flurbiprofen in ethanol containing 0.1-10% of a co-solvent such that the effective dose is in the range 0.5 to 10 mg per cm² of absorbent material in contact with the skin and wherein the absorbent material has a second surface, opposite

25 the first, provided with an impermeable backing layer of polyethylene, and further wherein the absorbent material is sealed in an impermeable pouch.

- 25 -

10. A formulation as claimed in claim 1 suitable for use as a wrap-around having a first surface, to be placed in contact with the skin, with an area in the range of 200-300 cm², wherein the absorbent material is
5 impregnated with a pharmaceutical composition comprising a 2.5-7.5% by weight of a solution of S(+)-flurbiprofen in ethanol containing 0.1-10% of a co-solvent such that the effective dose is in the range 0.5 to 10 mg per cm² of absorbent material in contact with the skin and
10 wherein the absorbent material has a second surface, opposite the first, provided with an impermeable backing layer of polyethylene, and further wherein the absorbent material is sealed in an impermeable pouch.

1/3

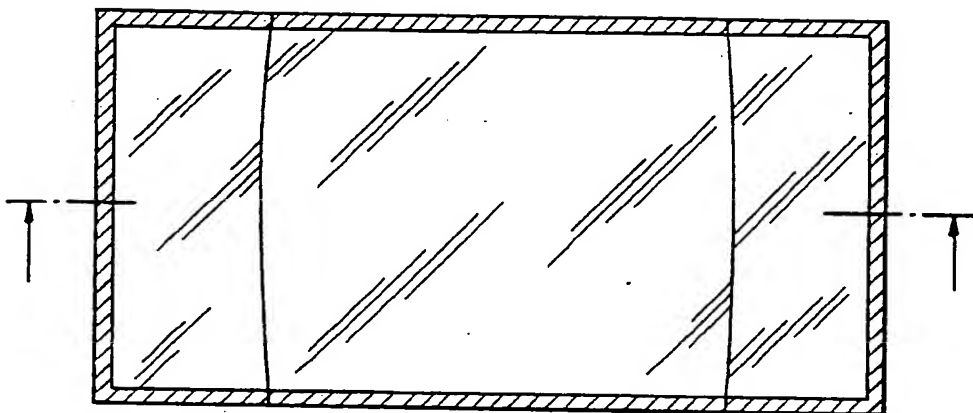


Fig. 1

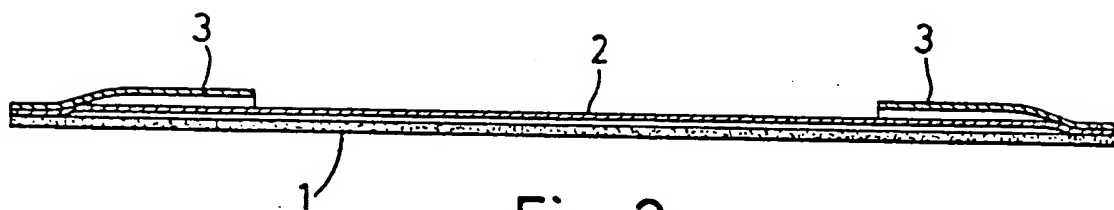


Fig. 2

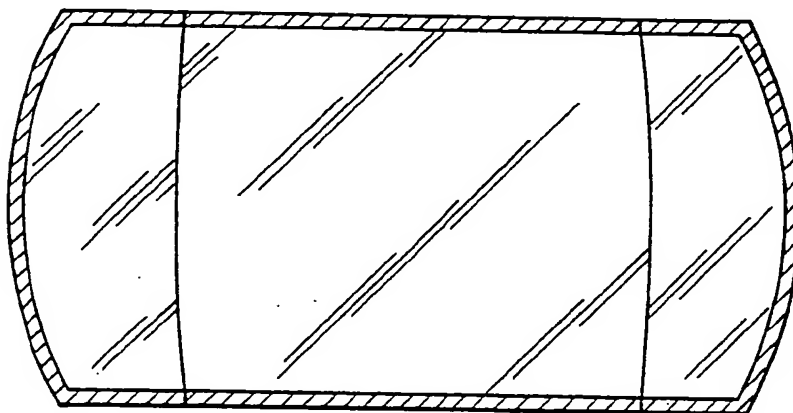


Fig. 3

2/3

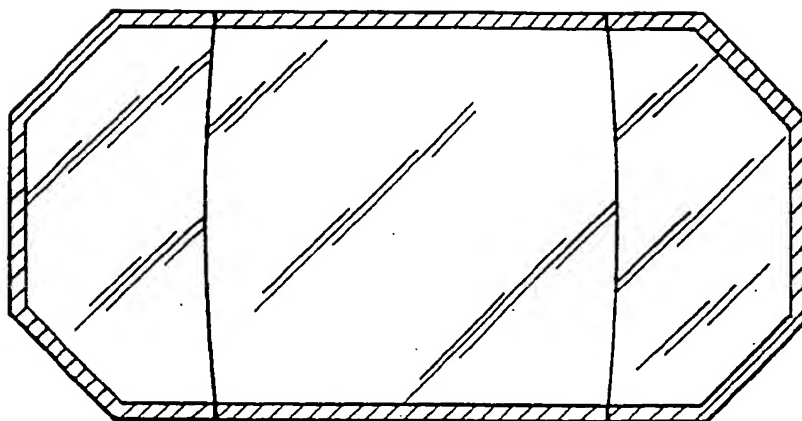


Fig. 4

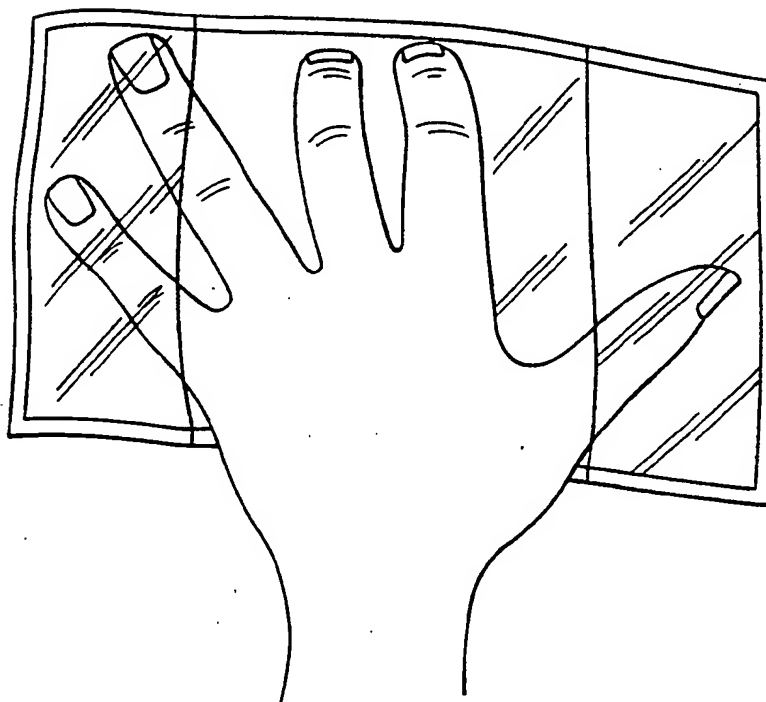


Fig. 5

3/3

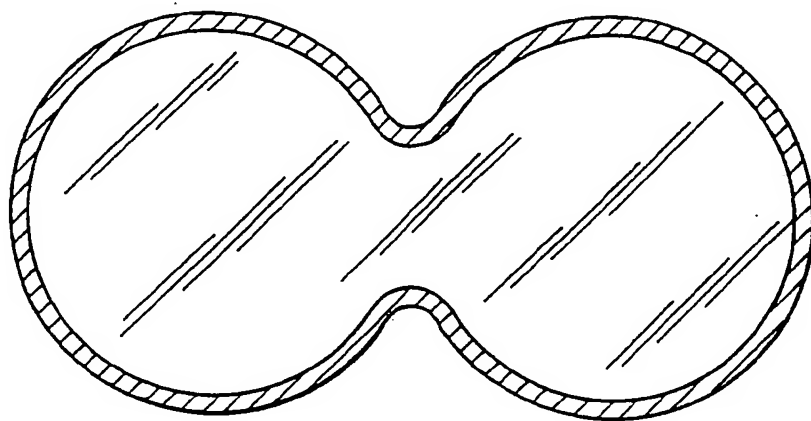


Fig. 6

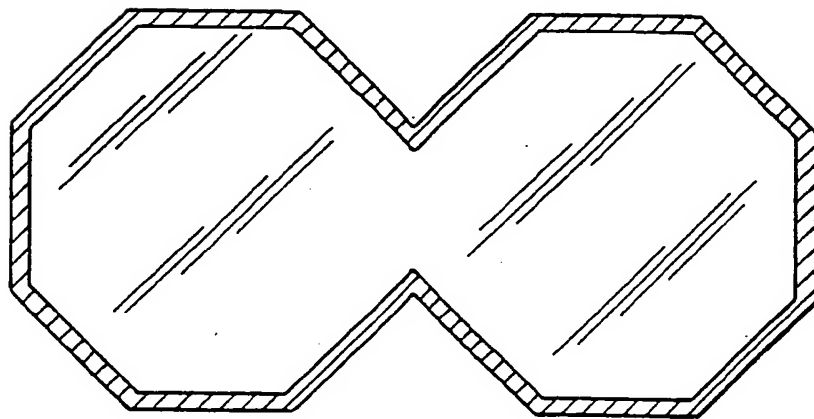


Fig. 7



Fig. 8

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/70 A61L15/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 05768 (ANALGESIC ASSOCIATES) 16 April 1992 cited in the application see page 16, line 15 - line 21 see page 17, line 6 - line 10 see page 18, line 13 --- -/--	1-3

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 June 1995

Date of mailing of the international search report

05. 07. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Boulois, D

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI Section Ch, Week 8705 Derwent Publications Ltd., London, GB; Class A12, AN 87-031748 & JP,A,61 275 212 (HISAMITSU PHARM. KK) , 5 December 1986 see abstract</p>	1,2,4
X	<p>& PATENT ABSTRACTS OF JAPAN vol. 01 no. 136 (C-419) ,3 April 1987 & JP,A,61 275212 (HISAMITSU PHARM. CO INC) 5 December 1986, see abstract</p>	1,2,4
X	<p>GB,A,119 646 (HENGEVELD H.) 7 April 1919 see the whole document</p>	1,3
A	<p>FR,A,2 500 301 (KOWA CO LTD) 27 August 1982 see page 4, line 14 - line 20 see page 14, line 32 - page 5, line 4 see page 12; example 1</p>	1,4
A	<p>US,A,5 061 724 (SHELDON GERTNER) 29 October 1991 see the whole document</p>	1
A	<p>FR,A,2 482 456 (HISAMITSU PHARM. CO INC) 20 November 1981 see page 6; example 8</p>	1
A	<p>CHEMICAL ABSTRACTS, vol. 111, no. 24, 11 December 1989 Columbus, Ohio, US; abstract no. 219316, TSUCHA Y. ET AL 'Bioavailability-improved transdermal ketoprofen solutions ' see abstract</p>	1
A	<p>& PATENT ABSTRACTS OF JAPAN vol. 13 no. 399 (C-632) & JP,A,01 143831 (NISSAN CHEM. IND LTD) 6 June 1989, see abstract</p>	1
A	<p>& DATABASE WPI Section Ch, Week 8928 Derwent Publications Ltd., London, GB; Class A03, AN 89-204082 & JP,A,01 143 831 (NISSAN CHEM. IND. KK) , 6 June 1989 see abstract</p>	1

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 110, no. 14, 3 April 1989 Columbus, Ohio, US; abstract no. 121414, ISHIDA KENJI 'Manufacture of bandages coated with pharmaceuticals ' see abstract	1
A	& DATABASE WPI Section Ch, Week 8823 Derwent Publications Ltd., London, GB; Class A12, AN 88-158813 & JP,A,63 099 866 (ISHIDA K.) , 2 May 1988 see abstract	1
A	EP,A,0 206 291 (KLINGE PHARMA GMBH) 30 December 1986 cited in the application see page 5 - page 6; examples 4,5	1
A	EP,A,0 331 382 (PFIZER INC) 6 September 1989 see page 18, line 28 - line 36	1
A	EP,A,0 439 344 (MC NEIL PPC INC) 31 July 1991 see page 5; example 1	1

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9205768	16-04-92	AU-A- 7850491	10-12-91
		AU-A- 8927191	28-04-92
		WO-A- 9117740	28-11-91
<hr/>			
GB-A-119646		NONE	
<hr/>			
FR-A-2500301	27-08-82	JP-C- 1683164	31-07-92
		JP-B- 3031686	08-05-91
		JP-A- 57140711	31-08-82
		BE-A- 892269	16-06-82
		CA-A- 1187414	21-05-85
		DE-A- 3206788	30-09-82
		GB-A, B 2096890	27-10-82
		NL-A- 8200695	16-09-82
		SE-B- 456720	31-10-88
		SE-A- 8201202	27-08-82
		US-A- 4440778	03-04-84
<hr/>			
US-A-5061724	29-10-91	EP-A- 0565530	20-10-93
		WO-A- 9308813	13-05-93
<hr/>			
FR-A-2482456	20-11-81	JP-B- 1035805	27-07-89
		JP-C- 1549867	09-03-90
		JP-A- 56161323	11-12-81
		JP-A- 56161324	11-12-81
		DE-A- 3119017	18-03-82
		GB-A, B 2075837	25-11-81
		US-A- 4393076	12-07-83
<hr/>			
EP-A-206291	30-12-86	DE-A- 3522550	02-01-87
		US-A- 4704406	03-11-87
<hr/>			
EP-A-331382	06-09-89	CA-A- 1331137	02-08-94
		ES-T- 2051998	01-07-94
		FI-C- 92650	27-12-94
		FI-B- 92650	15-09-94
		JP-A- 2003613	09-01-90
		PT-B- 89837	31-01-94
		US-A- 4959365	25-09-90
		US-A- 5196410	23-03-93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-331382		US-A- 5391548	21-02-95
EP-A-439344	31-07-91	US-A- 5093133	03-03-92
		AU-B- 632655	07-01-93
		AU-A- 6991991	25-07-91
		GR-B- 1001025	31-03-93
		JP-A- 4210914	03-08-92

THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☒ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☒ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)